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Complete List of Authors:	Been, Jasper; Erasmus MC, Neonatology Mackay, Danny; University of Glasgow Millett, Christopher; School of Public Health, Imperial College, Department of Primary Care and Public Health Soyiri, Ireneous van Schayck, Constant; Maastricht University, HAG Pell, Jill; University of Glasgow, Public Health Sheikh, Aziz; University of Edinburgh, Community Health Sciences
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Smoke-free legislation and paediatric hospitalisations for acute respiratory tract infections: national quasi-experimental study with unexpected findings and important methodological implications

Jasper V. Been[1-3]*, Daniel F. Mackay[4], Christopher Millett[5], Ireneous Soyiri[2], Constant P. van Schayck[2,3], Jill P. Pell[4], Aziz Sheikh[2,3,6]

*Corresponding author: Division of Neonatology, Department of Paediatrics, Erasmus MC – Sophia Children's Hospital, PO Box 2060, 3000 CB Rotterdam, Netherlands; E: j.been@erasmusmc.nl; T: +31-10-7036583; F: +31-10-7036542.

[1]Division of Neonatology, Department of Paediatrics, and Department of Obstetrics and Gynaecology, Erasmus MC – Sophia Children's Hospital, Rotterdam, Netherlands; j.been@erasmusmc.nl

[2]Centre of Medical Informatics, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK; i.soyiri@ed.ac.uk; a.sheikh@ed.ac.uk

[3]School for Public Health and Primary Care, Maastricht University, Maastricht, Netherlands

[4]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK; daniel.mackay@glasgow.ac.uk; jill.pell@glasgow.ac.uk

[5]Public Health Policy Evaluation Unit, School of Public Health, Imperial College London, London, UK; c.millett@imperial.ac.uk

[6]Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, 3rd Floor, 1620 Tremont Street, Boston MA, USA

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What this paper adds

What is already known on this subject

Implementation of comprehensive smoke-free legislation is associated with significant early-life health benefits, including reductions in severe paediatric respiratory events.

Evidence on the impact of national policies typically is derived from quasi-experimental studies; given their inherent risks of bias and confounding, replication of such studies across various settings is essential.

What this study adds

We investigated if the March 2006 national implementation of comprehensive smoke-free legislation in Scotland was associated with a reduction in hospital admissions/deaths due to acute respiratory tract infections among children.

Our pre-specified interrupted time series approach suggested that implementation of smoke-free legislation in Scotland was associated with an increase in paediatric respiratory tract infection admissions/deaths.

We were concerned that this result, which contradicted published evidence, was spurious. The association was indeed reversed when accounting for an unanticipated antecedent breakpoint in the temporal trend, suggesting that the legislation may in fact be protective.

We discuss the findings from this national study and propose approaches to enhancing the methodological quality of interrupted time series studies.

ABSTRACT

Objectives

We investigated whether Scottish implementation of smoke-free legislation was associated with a reduction in unplanned hospitalisations or deaths ('events') due to respiratory tract infections (RTIs) among children.

Design

Interrupted times series (ITS)

Setting/participants

Children aged 0-12 years living in Scotland during 1996-2012

Intervention

National comprehensive smoke-free legislation (March 2006)

Main outcome measure

Acute RTI events in the Scottish Morbidity Record-01 and/or National Records of Scotland Death Records

Results

135,134 RTI events were observed over 155 million patient-months. In our pre-specified negative binomial regression model accounting for underlying temporal trends, seasonality, sex, age group, region, urbanisation level, socioeconomic status, and seven-valent pneumococcal

vaccination status, smoke-free legislation was associated with an immediate rise in RTI events (incidence rate ratio (IRR)=1.24, 95%CI 1.20-1.28) and an additional gradual increase (IRR=1.05/year, 95%CI 1.05-1.06). Given this unanticipated finding we conducted a number of post-hoc exploratory analyses. Among these, automatic breakpoint detection indicated that the rise in RTI events actually preceded the smoke-free law by 16 months. When accounting for this breakpoint, smoke-free legislation was associated with a gradual decrease in acute RTI events: IRR=0.91/year, 95%CI 0.87-0.96.

Conclusions

Our pre-specified ITS approach suggested that implementation of smoke-free legislation in Scotland was associated with an increase in paediatric RTI events. We were concerned that this result, which contradicted published evidence, was spurious. The association was indeed reversed when accounting for an unanticipated antecedent breakpoint in the temporal trend, suggesting that the legislation may in fact be protective. ITS analyses should be subjected to comprehensive robustness checks to assess consistency.

BACKGROUND

Tobacco smoking continues to cause a considerable burden of death and disease worldwide.[1,2] It is estimated that 40-50% of children globally are regularly exposed to second-hand smoke (SHS).[3,4] They are particularly vulnerable to the adverse effects of SHS exposure as their bodies are still undergoing development and, especially when very young, cannot influence their own degree of exposure. Among children under five years of age, exposure to SHS has been estimated to cause 165,000 deaths and almost six million disability-adjusted life years (DALYs) annually through lower respiratory tract infections (RTIs) alone.[3] Additional adverse paediatric health outcomes associated with SHS exposure include otitis media with effusion,[5] invasive meningococcal disease,[6] and wheezing disorders including asthma.[7,8]

There is a pressing need to identify effective approaches to reducing child SHS exposure and through so doing improve child health. The effectiveness of individual or family-level interventions to reduce SHS exposure has generally been disappointing.[9] At a population level, governmental policies aimed at reducing tobacco smoking and SHS exposure have the potential to also reduce child SHS exposure. Comprehensive smoke-free laws and tobacco tax increases have been shown to be associated with improved respiratory health among children.[10-13] Evaluation of the effectiveness of such policies is however complicated by the fact that they are generally not amendable to implementation in a randomised fashion.[14]

Quasi-experimental studies, such as interrupted time series (ITS) studies, are advocated as a next best alternative to randomised designs when evaluating the impact of population-level policy changes.[15] Attribution of causality is however challenging because of the inherent risks of bias

and confounding. Findings are in addition sensitive to choice and specification of the statistical modelling technique used. Pre-specification of a detailed statistical analysis plan has been advocated to reduce the associated risk of data dredging, to encourage publication irrespective of a study's findings, and to promote the reproducibility of science.[16,17]

We investigated whether the implementation of comprehensive smoke-free legislation in Scotland was associated with changes in the number of unplanned paediatric hospitalisations or deaths due to RTIs. Introduction of the Scottish smoke-free law was followed by significant reductions in reported SHS exposure in public places and the home environment among school-age children, along with a –40% (95%CI –47; –32, p<0.001) reduction in mean salivary cotinine concentrations.[18] Previous studies in England, Hong Kong and the United States have identified significant reductions in hospital admissions for acute RTIs among children following introduction of smoke-free laws.[10,12,19,20] Based on these previous studies and the wider evidence of the health impact of smoke-free legislation,[11,21-24] we hypothesised that the Scottish smoke-free law would be associated with a reduction in acute RTI events.

METHODS

This study was conducted according to a protocol developed *a priori* (National Services Scotland reference: PAC 04/12 IR – XRB13092; Supplementary File 1). We analysed the association between introduction of smoke-free legislation in Scotland and the incidence rate of unplanned hospital admissions or deaths due to acute RTIs among children aged ≤12 years. STROBE and RECORD statements were followed to guide reporting.Given use of fully anonymised routinely

collected health care data, we received an exemption from formal ethical assessment for this study.

Smoke-free legislation

On 26 March 2006, a national law came into force overnight in Scotland prohibiting smoking in enclosed public places (i.e. bars; restaurants; hotels; shops; shopping centres; libraries; archives; museums; galleries; entertainment premises (e.g. cinemas; concert halls; theatres; gaming and amusement arcades; discotheques); film studios; assembly halls; conference centres; exhibition halls; public toilets; clubs premises; educational institutions (e.g. schools); care homes and shelters; health care premises (e.g. hospitals); child care premises (e.g. nurseries); religious premises (e.g. churches); sports centres; public transportation facilities (e.g. airports) and vehicles; public telephone kiosks) and workplaces (including offshore facilities and work vehicles), with very few exemptions (i.e. residential accommodation; designated rooms in adult care homes and adult hospices; designated rooms in psychiatric hospitals and psychiatric units; designated hotel bedrooms; designated detention or interview rooms; designated laboratory rooms; Her Majesty's submarines and ships of the Royal Fleet Auxiliary; private vehicles).[25] Of inspected premises, 96-99% were compliant with the law in the first year following the law's introduction, and 94-97% and 95-97% in the second and third year, respectively.[26]

Study population and period

We included data from all children aged ≤12 years who were resident in Scotland at any time during the study period and had not yet experienced an RTI event before the study period. Children aged 13 years and above were excluded in an attempt to limit potential confounding by active smoking. We included data on all first unplanned hospital admissions or deaths due to

acute RTIs (composite outcome: 'events') occurring between 1 January 1996 and 31 December 2012 (i.e. the most recent data available at the time of data extraction).

Outcome definitions

Our primary outcome was the incidence rate of acute RTI events. Deaths were included to account for children that died due to an acute RTI before having reached the hospital. Secondary outcomes were the separate incidence rates of upper and lower RTI events. In these analyses, events that contained both a code for an upper and a lower RTI were counted as lower RTI events. For the purpose of this study, an event was considered to be associated with an acute RTI if this had been registered as either a primary or secondary diagnosis. The following International Classification of Diseases-10 codes were included: upper RTIs: A37, H66-67, J00-06, J09-11 (not J10.0/J11.0); lower RTIs: J10.0/J11.0, J12-18, J20-22, J40-42 (Supplementary File 2). To avoid contamination of our outcome of interest with asthma exacerbations which may or may not have been due to RTIs, events where asthma was recorded as the primary diagnosis were excluded. In order to prevent dependency of data due to individual children experiencing multiple RTI events during the study period, only first events (i.e. admission or death, whichever came first) were included. For eligible children born before start of the study period (i.e. 1 January 1996) a look-back period of 12 years was applied to determine whether the child previously experienced an acute RTI hospitalisation.

Data sources

Data on acute RTI hospitalisations were retrieved from the Scottish Morbidity Record 01 (SMR01), a national database collecting data on all hospital admissions among Scottish residents. Deaths due to acute RTIs were identified from National Records of Scotland Death Records. Data

on individual pneumococcal conjugate vaccine (PCV) vaccination status were retrieved from the Scottish Immunisation and Recall System database, which collects national vaccination data. Individual-level data were linked across the different databases by electronic Data Research and Innovation Service (eDRIS) staff at Information Services Division Scotland using the unique Community Health Index (CHI) identifier before being made available to the researchers. Air quality data were obtained from the UK Governmental Department for Environment Food and Rural Affairs (DEFRA) and linked to the main data document by the researchers.[27]

Data handling and covariates

The numbers of children at risk and those experiencing a first acute RTI event were aggregated by eDRIS staff into strata based on all possible combinations of the following covariates: month; year; sex (male; female); age group (<5 years; ≥5 years); region (according to health board of residence: South-West; South-East; North); urbanisation level (according to residential post code: urban; rural); socioeconomic status (quintiles of Scottish Index of Multiple Deprivation (SIMD [28]; 2006 version) based on residential postcode); PCV vaccination (yes; no). On 4 September 2006, PCV was introduced into the childhood immunisations schedule at two, four, and 13 months of age, with a catch-up programme for children born from 5 September 2004.[29] Given the close temporal proximity of PCV introduction to that of the smoke-free law in Scotland we linked data on RTI events to PCV vaccination status at an individual level to address potential confounding.[10]

In a post-hoc analysis we used air quality data for all Scottish monitoring sites that collected data during the study period: carbon monoxide (CO; mg/m^3); nitric oxide (NO; $\mu g/m^3$); nitrogen dioxide (NO_2; $\mu g/m^3$); nitrogen oxides as NO_2 ($\mu g/m^3$); sulphur dioxide (SO_2; $\mu g/m^3$); ozone (O_3;

μg/m^3); particulate matter of diameter <10μm (PM10; μg/m^3). For each monitoring site, mean monthly values were calculated from mean daily values and missing values were imputed using linear interpolation. Availability of air quality data from fixed stations was patchy both across time and the different monitoring sites, hampering combination of data across sites. Fairly consistent data throughout the study period was only available for Glasgow city centre.

Statistical analyses

Negative binomial regression analysis was pre-specified as our primary analysis, in which the number of acute RTI events was the dependent variable. Predictors included: time (a continuous variable ranging from '1' in January 1996 to '204' in December 2012, designed to account for the underlying temporal trend in acute RTI events); timing of the smoke-free law (a dummy variable coded '0' prior to March 2006 and '1' otherwise); an interaction variable 'time × smoke-free law' (to account for a change in temporal trend in acute RTI events following the law); month (a categorical variable to account for seasonality); sex; age group; region; urbanisation level; SIMD quintile; PCV vaccination. Akaike's information criterion (AIC) was used to select the optimal model among three options according to the temporal change in RTI events following the smoke-free law: immediate ('step') change; gradual ('slope') change; step + slope change. The size of the population at risk was used as an offset in the models. We modelled acute RTI events using three variants of negative binomial regression; NB1 (constant dispersion), NB2 (mean dispersion) and NBP ("NB *rho"*) which uses a second dispersion parameter that is allowed to vary freely across the data observations.[30] The most appropriate negative binomial variant was selected using AIC. We tested for non-linear time effects using a restricted cubic spline with four degrees of freedom compared with one degree of freedom using the 'mvrs' module in Stata.[31] In

November 2003 there was an unusually high incidence of RTI events, which was modelled using a dummy variable.

Post-hoc exploratory analyses

We performed a number of exploratory post-hoc analyses to assess the robustness of the findings from our primary analyses, which were felt to be implausible (discussed below).

First, we performed stratified analyses according to age group and sex to explore whether the association between smoke-free legislation and acute RTI events differed across categories of these variables. Young age and male sex are important risk factors for RTIs in childhood.

Second, we explored whether the association between smoke-free legislation and RTI events was robust to accounting for temporal trends in air quality. Given the patchiness of air quality availability, we performed an exploratory analysis adding Glasgow city centre air quality data as parameters to the model, using data on acute RTI events occurring in South-West Scotland only. Backward selection of air quality indicators was based on AIC.

Third, we ran time series regressions on the acute RTI events with seasonal autoregressive integrated moving average ((S)ARIMA) errors to account for regular and seasonal autoregression in the data. The models contained an underlying trend, a dummy variable for the post-ban period and a post-ban temporal trend, allowing a number of intervention effects to be tested. Again, we tested for non-linear time effects using Stata's 'mvrs' module.[31] Candidate error models were identified from autocorrelation and partial autocorrelation plots. The most appropriate model was selected using the AIC statistic and was subjected to standard diagnostic tests for white noise

residuals using the Ljung-Box Portmanteau statistic as well as graphically using auto-correlation plots and correlograms.[32]

Fourth, we tested for structural breaks in the time series data using Stata's 'estat sbsingle' command. The procedure searches for a possible trend break over a stipulated range of dates by calculating the value of the test statistic (Wald or likelihood ratio) at each date and then using the maximum value of the test statistic to identify the potential break.[33] For the test to work, the series needed to be trimmed prior to the search so as to avoid using dates too close to the end or beginning of the series which would result in breakdown of the procedure. After 20% trimming we tested for a break in the intercept (step change) as well as a break in the trend (slope change). As a test of robustness we used the econometrics software EViews to also check for a structural break using its comprehensive suite of breakpoint detection options with 20% trimming of the data. The selected breakpoint and its form (step and/or slope) was then included as an additional regressor in the negative binomial model and the models re-estimated.

All analyses were performed within the National Services Scotland's Safe Haven environment using Stata MP version 14 except for the (S)ARIMA models. These were analysed separately on aggregated data which were supplied to the authors by the NSS Safe Haven after statistical disclosure control. The (S)ARIMA models and the structural break analysis were developed using Stata SE version 14 with the structural break point further corroborated using EViews 9.5.

RESULTS

During 155 million patient-months of observation, 135,134 acute RTI events were recorded: 79,153 upper RTI events and 56,011 lower RTI events. There was substantial variation in the incidence rate of acute RTI events over time (Figure 1) and across demographic subgroups (Table 1).

Table 1. Demographic characteristics of children experiencing an acute respiratory tract infection event

Characteristic	Acute RTI events (n)			Mean monthly acute upper RTI event rate (per 1000 children)		
	Upper RTIs (n=79,153)	Lower RTIs (n=56,011)	All RTIs (n=135,134)	Upper RTIs (0.51)	Lower RTIs (0.36)	All RTIs (0.87)
Sex						
Male	46,116	31,912	78,028	0.58	0.40	0.98
Female	33,007	24,099	57,106	0.43	0.32	0.76
Age						
0-4 years	67,462	51,109	118,571	1.16	0.88	2.05
5-12 years	11,661	4,902	16,563	0.12	0.05	0.17
Region						
North	28,074	18,257	46,332	0.57	0.37	0.93
South-West	34,496	23,759	58,255	0.50	0.34	0.84
South-East	16,553	13,994	30,547	0.46	0.39	0.86
Urbanisation level						
Urban	64,939	46,739	111,678	0.51	0.37	0.89
Rural	14,184	9,272	23,456	0.49	0.32	0.81
Socio-economic status						
Quintile 1 (most affluent)	12,508	8,928	21,436	0.41	0.30	0.71
Quintile 2	14,507	9,693	24,200	0.48	0.32	0.81
Quintile 3	14,808	10,043	24,851	0.50	0.34	0.84
Quintile 4	16,849	11,658	28,507	0.57	0.39	0.96
Quintile 5 (most deprived)	20,451	15,689	36,140	0.58	0.45	1.03
PCV vaccination status						
PCV received	13,324	5,619	18,943	0.69	0.19	0.88
PCV not received	65,799	50,392	116,191	0.47	0.39	0.86

PCV = pneumococcal conjugate vaccine; RTI = respiratory tract infection

In our primary analysis, introduction of smoke-free legislation was associated with an immediate rise in acute RTI events (incidence rate ratio (IRR) 1.24, 95% confidence interval (CI) 1.20-1.28) and an additional gradual increase over time (IRR 1.06 per year, 95%CI 1.05-1.06; Table 2). This finding was consistent when upper and lower RTI events were considered separately (Table 1 and Supplementary File 3).

Post-hoc subgroup analyses to assess whether the unanticipated findings were confined to certain subgroups demonstrated consistency across sex and age subgroups (Supplementary File 4 and 5). In an analysis of data from South-West Scotland only, addition of mean monthly air quality indicators measured in Glasgow improved model performance (Supplementary File 6). This did not have a major bearing on the association between smoke-free legislation and acute RTI events: immediate change IRR 1.25, 95%CI 1.19-1.32; gradual change IRR 1.08 per year, 95%CI 1.06-1.10.

In further post-hoc analyses, the strength of association between timing of smoke-free legislation and acute RTI events was very similar when evaluated using a reg(S)ARIMA model of order AR(1,7) MAR(3,12): IRR 1.15, 95%CI 1.02-1.28. However, automatic breakpoint detection suggested that the increase in acute RTI events started well before introduction of smoke-free legislation – i.e. in November 2004 (Supplementary File 7). Using this breakpoint rather than timing of smoke-free legislation in the primary negative binomial regression analysis indeed improved model performance as compared to the primary model (Supplementary File 8). When timing of smoke-free legislation was then added to the model that included the November 2004 breakpoint, smoke free legislation was associated with a gradual decrease in acute RTI events (IRR 0.91 per year, 95%CI 0.87-0.96), with no evidence of a 'step' change at that time (Table 2).

Table 2. Multivariable negative binomial regression model for acute respiratory tract infection events

Characteristic	Event rate ratio (ERR (95%CI))	
	Primary model (pre-specified)	Post-hoc analysis
Time (per year increase)	1.01 (1.01-1.01)	0.99 (0.99-1.00)
Smoke-free legislation	1.24 (1.20-1.28)*	Dropped from model based on AIC
Time since smoke-free legislation (per year increase)	1.06 (1.05-1.06)*	0.91 (0.87-0.96)*
November 2004 breakpoint	Not in model	1.13 (1.08-1.19)
Time since November 2004 breakpoint (per year increase)	Not in model	1.16 (1.12-1.20)
Month (reference = January)		
February	0.83 (0.80-0.86)	0.83 (0.80-0.86)
March	0.78 (0.75-0.81)	0.78 (0.75-0.81)
April	0.54 (0.52-0.56)	0.54 (0.52-0.57)
May	0.52 (0.50-0.54)	0.52 (0.50-0.54)
June	0.46 (0.44-0.48)	0.46 (0.44-0.48)
July	0.33 (0.32-0.30)	0.33 (0.32-0.35)
August	0.29 (0.28-0.48)	0.29 (0.28-0.31)
September	0.47 (0.45-0.34)	0.47 (0.45-0.49)
October	0.57 (0.55-0.59)	0.57 (0.55-0.60)
November	0.84 (0.81-0.88)	0.85 (0.82-0.88)
December	1.26 (1.22-1.31)	1.27 (1.23-1.32)
Male sex (reference = female)	1.31 (1.28-1.33)	1.31 (1.28-1.33)
Age 5-12 years (reference = 0-4 years)	0.07 (0.07-0.08)	0.07 (0.07-0.08)
Region (reference = North)		
South-West	0.87 (0.85-0.89)	0.87 (0.85-0.89)
South-East	0.90 (0.89-0.92)	0.90 (0.89-0.92)
Living in urban area (reference = rural)	0.99 (0.97-1.01)	0.99 (0.98-1.01)
Socio-economic status (reference = Quintile 1; most affluent)		
Quintile 2	1.11 (1.09-1.14)	1.11 (1.08-1.14)
Quintile 3	1.14 (1.11-1.17)	1.14 (1.11-1.17)
Quintile 4	1.25 (1.22-1.29)	1.25 (1.22-1.29)
Quintile 5 (most deprived)	1.35 (1.32-1.39)	1.35 (1.31-1.39)
PCV vaccination received (reference = not received)	0.45 (0.43-0.46)	0.45 (0.43-0.46)

November 2003 (outlier)	1.48 (1.37-1.60)	1.61 (1.49-1.74)

AIC = Akaike's Information Criterion; PCV = pneumococcal conjugate vaccine

The post-hoc analysis includes adjustment for an additional breakpoint in November 2004; *p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine; RTI = respiratory tract infection

DISCUSSION

In this large national ITS study conducted according to a pre-specified analysis plan, introduction of comprehensive smoke-free legislation in Scotland was associated with a significant increase in paediatric RTI events. Findings from our exploratory post-hoc analyses, which were undertaken to further investigate this unexpected finding, however indicated that the increase in RTI events most likely preceded the legislation by 16 months, making a direct causal link between the legislation and increased risk of RTIs implausible.

Our study has a number of strengths. It was conducted according to a pre-defined protocol, including a detailed statistical analysis plan, which was developed *a priori* in an attempt to promote scientific transparency and reproducibility.[17] We used over 10 million patient-years of high-quality data routinely collected over a 17-year period. Virtual universal availability of the CHI number minimises risks of incorrect data linkage across the datasets. We accounted for underlying temporal trends in RTI events as well as changes in population size and demographic structure. We applied a look-back period to reduce bias from RTI events occurring prior to the

study period. Our modelling approach is widely applied in the evaluation of national public health interventions, including national smoke-free laws.[11,20,22,23]

Given these strengths, the implausible findings are of considerable concern. It is important to consider the limitations of the study to see if these may have contributed to the observed findings. Allocation of a nationwide intervention cannot be randomised, and a quasi-experimental approach is considered a potentially valid method to evaluate impact such interventions.[15] Re-analyses of cluster randomised controlled trials using an ITS approach have demonstrated that their findings can in fact be highly similar.[34-36] Whilst residual bias could possibly have influenced our findings,[14] we consider it unlikely that this would explain the implausible results of our primary analysis.

Results of our pre-specified primary analysis were unanticipated and contradicted prior evidence on the topic.[10,12,19] Studies in other countries, including in the UK, previously identified consistent associations between comprehensive smoke-free legislation and subsequent reductions in paediatric RTI hospitalisations.[10,12,19] In line with these studies, there is consistent evidence for reductions in severe asthma exacerbations among children and in respiratory admissions among adults following implementation of smoke-free laws.[11,20,22] Post-hoc analyses showed that our findings were consistent across demographic subgroups and unlikely to have resulted from residual confounding by air pollution. As findings from ITS studies have previously been reported to be sensitive to choice of the modelling approach,[37] we performed additional aggregate-level times series analyses, again confirming the findings of our primary analysis. Automatic breakpoint detection is a method to explore whether a change in the incidence of the outcome under study indeed co-occurred with the known timing of the

intervention, and its use has been promoted as a routine validity test in single-group ITS analyses.[38] Using such an approach in a previous study, Kabir and colleagues were able to pinpoint timing of the observed reduction in small-for-gestational-age births to introduction of comprehensive smoke-free legislation in Ireland.[39] Using two different approaches and software packages to perform automatic breakpoint detection in our time series, the unanticipated increase in RTI events was shown to have preceded the smoke-free law by 16 months. This earlier breakpoint corresponds quite closely with temporal trends in paediatric RTI hospitalisations in England, which rose a consistently from 2003 onwards.[40] In a previous study, implementation of English comprehensive smoke-free legislation in 2007 was associated with a reduction in paediatric RTI admissions when accounting for this rising underlying trend.[10] This closely corresponds to the findings of our post-hoc analysis in Scotland, where RTI events were shown to increase consistently from 2004 onwards, this rise being attenuated after implementation of smoke-free legislation. Whereas an exploration of the underlying causes of the increasing trend in RTI events in Scotland was outside the scope of our study, several potential explanations for the corresponding rise in England have been postulated at the levels of the carer (e.g. decreasing threshold to take children to primary care or straight into hospital for evaluation), the health professional (e.g. decrease in threshold for referral by primary care doctors or for hospital admission), and the health care system (e.g. introduction of four-hour waiting target at emergency departments, unintended financial incentives for admission).[40]

Perhaps the main value of this study therefore is that it uncovers a number of important methodological challenges, which have not previously received adequate attention in the applied ITS literature. We used advanced methods and followed a pre-specified analytical approach – including a detailed statistical analysis plan – in an attempt to promote transparency.[16,17,41]

Despite this, our study yielded findings which were implausible and highly likely to be spurious. We therefore conducted a number of exploratory post-hoc analyses, which added weight to our assessment that the findings of our primary analysis were indeed spurious. It is important to acknowledge that these post-hoc analyses were unlikely to have been conducted should the findings from our primary analysis have confirmed our initial hypothesis. In such a scenario, our study would still have biased the literature on the topic.

At present, most public policy interventions remain unevaluated. ITS studies are arguably the most robust approaches we have at our disposal to evaluate the public health impact of these major experiments, which are seldom amendable to being implemented in a randomised fashion.[14] Despite their limitations, there is thus a need for many more ITS studies to be undertaken to continue to inform policy making at national, regional and global levels. To address the issues highlighted by our study, we propose that future ITS studies evaluating public health interventions should analyse the association under study using a number of different modelling approaches; ideally these should be pre-specified and include approaches based on both individual and aggregate level data (i.e. formal time series approaches). Also, we recommend that automatic breakpoint detection approaches are included to validate temporal co-occurrence of the intervention and the change in the outcome under study. This and other machine learning approaches are likely to become increasingly applicable in discerning unusual patterns in time series data over and above variations due to natural changes and those explained by temporal, environmental, and individual-level confounding.[38] Confidence in the results from individual ITS studies can be further increased by reproducing findings in other settings, and interpreting findings from individual studies in the light of the totality of evidence on the topic.

Going back to the primary hypothesis under investigation, we are reluctant to draw firm conclusions on the impact of Scotland's smoke-free legislation on paediatric RTIs given the inconsistent findings of the various analyses. Building on the existing evidence base on the topic,[20-24] we feel it is highly unlikely that smoke-free legislation was indeed responsible for a rise in paediatric RTI events, as our primary analyses seemed to suggest. On the other hand, given these findings it is also difficult to be confident that the result of our additional exploratory analyses – which were post hoc – provides a more valid representation of the actual impact of the legislation.

Given the continuing need for formal quasi-experimental evaluations of public health interventions to inform policy making, we propose additional steps to improve the robustness of such studies, including: exploring the association between the intervention and outcome using a number of different (pre-specified) modelling approaches; analysing time series using both individual- and aggregate-level approaches; assessing for potential confounding by unmeasured factors; and using automatic breakpoint detection or alternative machine learning approaches to scrutinise findings from pre-specified primary analyses, irrespective of whether these support the underlying hypothesis. We hope that the lessons drawn from this experience will increase the validity of future ITS studies in the medical and public health literature.

Contributor Statement

JVB conceived the study, obtained funding, developed the methods, analysed the data, interpreted the findings, and drafted the manuscript. DFM developed the methods, analysed the data, interpreted the findings, and contributed to drafting the manuscript. CM, CPvS, and JPP developed the methods, interpreted the findings, and provided feedback on the manuscript. IS extracted data, interpreted the findings, and provided feedback on the manuscript. AS conceived the study, obtained funding, developed the methods, interpreted the findings, and supervised drafting of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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References

1. World Health Organization. WHO report on the global tobacco epidemic, 2017. Monitoring tobacco use and prevention policies. 2017. http://www.who.int/tobacco/global_report/2017/en/. Accessed 6 October 2017.
2. US Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. 2014. https://www.surgeongeneral.gov/library/reports/50-years-of-progress. Accessed 6 October 2017.
3. Oberg M, Jaakkola MS, Woodward A, et al. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. *Lancet* 2011;377:139-46.
4. Mbulo L, Palipudi KM, Andes L, et al. Secondhand smoke exposure at home among one billion children in 21 countries: findings from the Global Adult Tobacco Survey (GATS). *Tob Control* 2016;25:e95-100.
5. Jones LL, Hassanien A, Cook DG, et al. Parental smoking and the risk of middle ear disease in children: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med* 2012;166:18-27.
6. Murray RL, Britton J, Leonardi-Bee J. Second hand smoke exposure and the risk of invasive meningococcal disease in children: systematic review and meta-analysis. *BMC Public Health* 2012;12:1062.
7. Tinuoye O, Pell JP, Mackay DF. Meta-analysis of the association between secondhand smoke exposure and physician-diagnosed childhood asthma. *Nicotine Tob Res* 2013;15:1475-83.

8. Vardavas CI, Hohmann C, Patelarou E, et al. The independent role of prenatal and postnatal exposure to active and passive smoking on the development of early wheeze in children. *Eur Respir J* 2016;48:115-24.

9. Baxi R, Sharma M, Roseby R, et al. Family and carer smoking control programmes for reducing children's exposure to environmental tobacco smoke. *Cochrane Database Syst Rev* 2014;p3:CD001746.

10. Been JV, Millett C, Lee JT, et al. Smoke-free legislation and childhood hospitalisations for respiratory tract infections. *Eur Respir J* 2015;46:697-706.

11. Been JV, Nurmatov UB, Cox B, et al. Effect of smoke-free legislation on perinatal and child health: a systematic review and meta-analysis. *Lancet* 2014;383:1549-60.

12. Lee SL, Wong WH, Lau YL. Smoke-free legislation reduces hospital admissions for childhood lower respiratory tract infection. *Tob Control* 2016;25:e90-e94.

13. Ma ZQ, Kuller LH, Fisher MA, et al. Use of interrupted time-series method to evaluate the impact of cigarette excise tax increases in Pennsylvania, 2000-2009. *Prev Chronic Dis* 2013;10:E169.

14. Been JV, Sheikh A. Investigating the link between smoke-free legislation and stillbirths. *Expert Rev Respir Med* 2016;10:109-12.

15. Kontopantelis E, Doran T, Springate DA, et al. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ* 2015;350:h2750.

16. Thomas L, Peterson ED. The value of statistical analysis plans in observational research: defining high-quality research from the start. *JAMA* 2012;308:773-4.

17. Ioannidis JP. How to make more published research true. *PLoS Med* 2014;11:e1001747.

18. Akhtar PC, Currie DB, Currie CE, et al. Changes in child exposure to environmental tobacco smoke (CHETS) study after implementation of smoke-free legislation in Scotland: national cross sectional survey. *BMJ* 2007;335:545.

19. Hawkins SS, Hristakeva S, Gottlieb M, et al. Reduction in emergency department visits for children's asthma, ear infections, and respiratory infections after the introduction of state smoke-free legislation. *Prev Med* 2016;89:278-85.

20. Faber T, Kumar A, Mackenbach JP, Millett C, Basu S, Sheikh A, Been JV. Tobacco control policies and perinatal and child health: a systematic review and meta-analysis. *Lancet Public Health* 2017;2:e420-37.

21. Faber T, Been JV, Reiss IK, et al. Smoke-free legislation and child health. *NPJ Prim Care Respir Med* 2016;26:16067.

22. Tan CE, Glantz SA. Association between smoke-free legislation and hospitalizations for cardiac, cerebrovascular, and respiratory diseases: a meta-analysis. *Circulation* 2012;126:2177-83.

23. Frazer K, Callinan JE, McHugh J, et al. Legislative smoking bans for reducing harms from secondhand smoke exposure, smoking prevalence and tobacco consumption. *Cochrane Database Syst Rev* 2016;2:CD005992.

24. Hoffman SJ, Tan C. Overview of systematic reviews on the health-related effects of government tobacco control policies. *BMC Public Health* 2015;15:744.

25. The prohibition of smoking in certain premises (Scotland) regulations 2006. 2006. http://www.gov.scot/Publications/2005/08/02143247/32478. Accessed 24 July 2017.

26. UK Web Archive. Clearing the air. Latest situation. Smoke-free legislation - national compliance data: summary. 2015.

https://www.webarchive.org.uk/wayback/archive/20150309182815/http://www.clearingtheairscotland.com/latest/index.html. Accessed 25 March 2017.

27. Department for Environment Food and Rural Affairs UK-AIR: Air Information Resource. https://uk-air.defra.gov.uk. Accessed 25 March 2017.

28. Scottish Government. The Scottish Index of Multiple Deprivation. http://www.gov.scot/Topics/Statistics/SIMD. Accessed 27 July 2017.

29. Pneumococcal conjugate vaccine catch-up campaign. 2015. http://www.isdscotland.org/Health-Topics/Child-Health/Immunisation/Pneumococcal-Conjugate-Vaccine.asp. Accessed 25 March 2017.

30. Hardin JW, Hilbe JM. Regression models for count data based on the negative binomial (p) distribution. *Stata J* 2014;14:280-91.

31. Royston P, Sauerbrei W. Multivariable modeling with cubic regression splines: A principled approach. *Stata J* 2007;7:45-70.

32. wntestq - Portmanteau (Q) test for white noise. Available from: http://www.stata.com/manuals13/tswntestq.pdf. Accessed 25 March 2017.

33. estat sbsingle - Test for a structural break with an unknown break date. Available from: http://www.stata.com/manuals14/tsestatsbsingle.pdf. Accessed 25 March 2017.

34. Fretheim A, Soumerai SB, Zhang F, et al. Interrupted time-series analysis yielded an effect estimate concordant with the cluster-randomized controlled trial result. *J Clin Epidemiol* 2013;66:883-7.

35. Fretheim A, Zhang F, Ross-Degnan D, et al. A reanalysis of cluster randomized trials showed interrupted time-series studies were valuable in health system evaluation. *J Clin Epidemiol* 2015;68:324-33.

36. St.Clair T, Hallberg K, Cook TD. The validity and precision of the comparative interrupted time-series design: three within-study comparisons. *J Educ Behav Stat* 2016;41:269-99.

37. Huesch MD, Ostbye T, Ong MK. Measuring the effect of policy interventions at the population level: some methodological concerns. *Health Econ* 2012;21:1234-49.

38. Linden A, Yarnold PR. Using machine learning to identify structural breaks in single-group interrupted time series designs. *J Eval Clin Pract* 2016;22:851-55.

39. Kabir Z, Daly S, Clarke V, et al. Smoking ban and small-for-gestational age births in Ireland. *PLoS One* 2013;8:e57441.

40. Gill PJ, Goldacre MJ, Mant D, et al. Increase in emergency admissions to hospital for children aged under 15 in England, 1999-2010: national database analysis. *Arch Dis Child* 2013;98:328-34.

41. International Epidemiological Association. Good Epidemiological Practice (GEP). IEA Guidelines for Proper Conduct in Epidemiologic Research. 2010. http://ieaweb.org/good-epidemiological-practice-gep. Accessed 25 March 2017.

Figure legend

Figure 1. Monthly time series of acute respiratory tract infection (RTI) event rates. Dashed grey line indicates introduction of smoke-free legislation.

Supplementary Files

Supplementary File 1: Study protocol

Supplementary File 2: List of ICD-10 codes

Supplementary File 3: Table S1. Multivariable negative binomial regression model for acute upper and lower respiratory tract infection events

Supplementary File 4: Table S2. Multivariable negative binomial regression model for acute respiratory tract infection events stratified according to sex

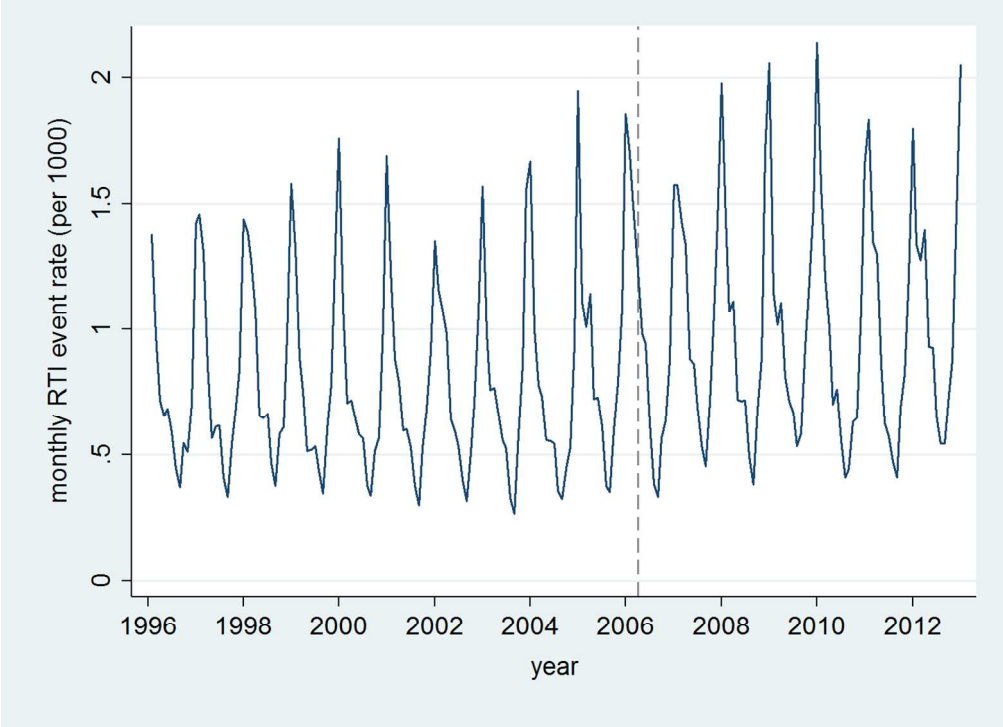
Supplementary File 5: Table S3. Multivariable negative binomial regression model for acute respiratory tract infection events stratified according to age group

Supplementary File 6: Table S4. Multivariable negative binomial regression model for acute respiratory tract infection events in South-East Scotland with adjustment for air quality

Supplementary File 7: Figure S1. Automatic breakpoint detection in trimmed time series of acute respiratory tract infection (RTI) events. The likelihood ratio (LR) test statistic

maximises in November 2004, indicating the most likely breakpoint in the time series. Dashed grey line indicates introduction of smoke-free legislation.

Supplementary File 8: Table S5. Multivariable negative binomial regression model for acute respiratory tract infection events with November 2004 breakpoint instead of timing of smoke-free legislation



Monthly time series of acute respiratory tract infection (RTI) event rates. Dashed grey line indicates introduction of smoke-free legislation.

511x371mm (72 x 72 DPI)

Supplementary Text S1: Study protocol

This study protocol was part of an application to the National Health Service National Services Scotland Privacy Advisory Committee (PAC 04/12 IR – XRB13092).

What is the background to the study?

Respiratory infections in childhood are one of the commonest reasons for hospital admission, primarily among infants. There is clear evidence that both antenatal and postnatal second-hand smoke (SHS) exposure increase the risk of respiratory infections among children. The relative contribution of SHS exposure to paediatric respiratory infections is greater than for childhood asthma, and adult lung cancer and cardiovascular disease for example. Worldwide the vast majority of the estimated 165,000 childhood deaths each year associated with SHS exposure are due to respiratory infections.

In Europe, over 50 percent of all children are regularly exposed to SHS. Particularly young children, who are most at risk of developing respiratory infections, have no means of controlling their own degree of SHS exposure and are therefore largely dependent on rules and regulations. However, despite World Health Organization (WHO) recommendations to implement smoke-free environments as part of a comprehensive approach to reduce SHS exposure, only 11% of countries had done so by 2010.

Why is the study needed?

Epidemiologic evaluations have shown reductions in asthma hospitalisations as well as preterm birth following the introduction of smoke-free legislation in different countries. To the best of our knowledge, the effect on respiratory tract infections has not been studied. Given the huge disease burden of

respiratory tract infections in childhood and the clear and important association between SHS exposure and respiratory infections in childhood, smoke-free legislation may carry important health benefit in this area. A better estimate of the range of effects that smoke-free legislation may have on paediatric health can serve as a mandate to further enhance the enforcement of measures to protect young people worldwide from the adverse effects of SHS exposure.

What are the aims and objectives of the study?

We aim to investigate the association between introduction of smoke-free legislation in Scotland (26 March 2006) and incidence changes in hospitalisations for acute respiratory infections among children aged 0-12 years.

Give a brief outline of the study design and data sources involved.

Study design

Interrupted time series

Time period

Hospitalisations or deaths associated with respiratory infections in children aged 12 years or under at that time occurring between January 1, 1996 and December 31, 2012 are included in the study.

Population

All first unplanned hospitalisations or deaths (together: 'events') associated with acute respiratory infections among children aged 12 years or under at that time are included in the given study period. A hospitalisation or death is considered to be associated with a respiratory infection if such is recorded as

either a primary or secondary diagnosis at the event. Deaths are included to account for children that died before reaching the hospital. Planned hospitalisations (e.g. for ear, nose, and throat (ENT) surgery) and hospitalisations for chronic upper respiratory infections are excluded. Furthermore, to prevent overlap with a previous study evaluating asthma hospitalisations (Mackay et al. NEJM 2010), all hospitalisation where asthma is recorded as the primary diagnosis are excluded. Children aged 13 years and above are excluded in an attempt to limit the potential confounding effect of self-smoking.

Outcome

The primary outcome is the number of first events associated with any acute respiratory infection. All hospitalisations and deaths where an acute respiratory tract infection is recorded as either a primary or a secondary diagnosis are included. Secondary outcomes include the number of events associated with acute upper respiratory tract infections, and the number of events associated with acute lower respiratory tract infections. A list of diagnostic international classification of diseases (ICD)-codes is attached as an appendix to the original protocol.

In order to prevent dependency of data, only first events for each child will be included in the dataset. Subsequent hospitalisations or death in a child that has previously been hospitalised are thus excluded. For children entering the study at the start of the study period (i.e. 1 January 1996) a look back period of 12 years will be applied to determine whether the child has experienced a hospitalisation for a respiratory infection prior to study entry.

Covariates

The following covariates will be included in the study: sex, age group, PCV immunisation status, month of admission, region, urban/rural setting, socioeconomic status (SES).

On 4 September 2006 PCV was introduced into the childhood immunisations schedule. Although the relative contribution of true pneumococcal infections to the total burden of admissions for respiratory infections, the majority of which is likely to be of viral aetiology, is expected to be small, the close temporal proximity of PCV introduction to that of the smoking ban necessitates adjustment for a potential confounding effect of vaccine exposure. Therefore SMR01 data will be linked to SIRS on an individual level and timed PCV immunisation status will be added as a potential confounder to the analyses.

Three regions of residence will be considered based on the following grouping of local health boards: southwest (Ayrshire, Greater Glasgow and Clyde, Dumfries and Galloway, Lanarkshire), southeast (Lothian, Borders, Forth Valley), and north (Grampian, Highland, Tayside, Fife, Island). Urban or rural setting will be based on the 2006 Scottish Executive Urban Rural Classification system. SES will be categorised into quintiles according to the 2006 Scottish Index of Multiple Deprivation (SIMD).

Dataset and items

Data on emergency hospital admissions or deaths associated with respiratory infections will be extracted from the Scottish Morbidity Record 01 (SMR01). The following data items will be extracted: data of birth (DOB), sex (SEX), postcode (PC), hospital code (INSTCODE), admission date (ADMDATE), admission type (ADMTYPE), admission/transfer from (ADMTFM), main and secondary conditions (DG1-2), discharge type (DISTYPE). Data will be linked on an individual basis via the community health index (CHI) number to the Scottish Immunisation and Recall System (SIRS) for ascertainment of PCV immunisation status.

Relevant data will be aggregated and provided in tabular form by ISD as follows. After data linkage on individual level, strata will be formed based on combinations of the different covariates (associated levels in brackets): sex (male/female); age group (<5 years/≥5 years); region (southwest/southeast/north); urbanisation level (urban/rural); SES (five quintiles as per SIMD); PCV

vaccination (yes/no); month (12 levels); year (1996-2012: 17 levels). Thus, 2×2×3×2×5×2×12×17=48,960 strata are formed. Event counts as well as population counts will be calculated and provided for each stratum. A table demonstrating final data structure is attached as an appendix to the original study protocol.

Sample size

Sample size calculation for time-oriented analyses is complicated given the complexity of the models, and in a way redundant given that nationwide data are being used for the current study. To the best of our knowledge, no prior studies in any other region have evaluated changes in the number of hospital admissions for respiratory infections among children following the introduction of smoke-free legislation.

In a previous epidemiological evaluation of the Scottish smoking ban a highly significant ($p<0.001$) annual drop in asthma hospitalisations of 13% was found among children <15 years of age. Meta-analyses of observational studies indicate that second hand smoke exposure is associated with higher risk of respiratory tract infections in infancy (OR 1.54 (95% CI 1.40-1.69) for lower respiratory tract infections in infancy and 1.62 (95% CI 1.33-1.97) for middle ear disease in childhood) when compared to incident and current asthma in children (OR 1.21 (95% CI 1.08-1.36), and 1.30 (95% CI 1.22-1.39), respectively). This indicates that smoke-free legislation is likely to have a larger effect on acute respiratory infections than asthma. Furthermore, paediatric hospital admissions for acute respiratory infections are more common than for asthma, and the study period for the current study is longer than compared to the previous asthma study. Therefore, we expect the current study to have ample power to detect a significant and clinically relevant drop in hospitalisations for respiratory infections, if present.

Statistical analyses

Univariate analyses

Population-level incidence trends ('counts') will be plotted over time to identify any apparent temporal changes. Interrupted time series analysis using negative binomial regression will be used to study the association of time trends in the outcomes of interest and introduction of smoke-free legislation. The analyses will allow for a sudden ('step') and a trend ('slope') change in incidence trends of each of the outcomes following 26 March 2006 (i.e. when the smoking ban came into force). Stratum-specific mid-year population estimates will be used to define the denominator for the analyses.

Multivariate analyses

Potential confounding will be adjusted for by formation of demographic subgroups and subsequent stratified analysis. Potential confounders include: sex, age, PCV immunisation status, region, urban/rural setting, and SES. Month of admission will be added to the model to account for seasonal variation in hospital admissions for respiratory infections. Aikake's and Bayesian information criterions will be used for final model selection. A combination of Hosmer-Lemeshow statistic and receiver operating characteristic (ROC)-curves will be used to assess model performance for logistic regression models.

Software

All analyses will be performed using Stata 12.1.

Supplemental File 2:

International Classification of Diseases (ICD)-10 codes used to define respiratory tract infection (RTI) events

upper RTIs:

A37	whooping cough
H66/67	suppurative and unspecified otitis media
J00	acute nasopharyngitis
J01	acute sinusitis
J02	acute pharyngitis
J03	acute tonsillitis
J04	acute laryngitis
J05	acute tracheitis
J06	acute upper respiratory infections of multiple or unspecified sites
J09-11 (not J10.0/J11.0)	influenza

lower RTIs:

J10.0/J11.0	influenza with pneumonia
J12	viral pneumonia
J13	pneumococcal pneumonia
J14/15	other bacterial pneumonia
J16/17	pneumonia due to other specified organism
J18	pneumonia, organism unspecified
J20	acute bronchitis
J21	acute bronchiolitis
J22	unspecified acute lower respiratory infection
J40/41/42	bronchitis

Supplementary Table S1. Multivariable negative binomial regression model for acute upper and lower respiratory tract infection events

Characteristic	Event rate ratio (ERR (95%CI))	
	Acute upper RTIs	Acute lower RTIs
Time (per year increase)	1.01 (1.00-1.01)	1.02 (1.01-1.03)
Smoke-free legislation	1.22 (1.19-1.26)*	1.23 (1.18-1.30)*
Time since smoke-free legislation (per year increase)	Dropped from model based on AIC	1.12 (1.11-1.13)*
Month (reference = January)		
February	0.98 (0.94-1.02)	0.71 (0.67-0.75)
March	1.07 (1.03-1.11)	0.53 (0.51-0.56)
April	0.81 (0.78-0.84)	0.32 (0.30-0.33)
May	0.82 (0.79-0.86)	0.27 (0.25-0.28)
June	0.75 (0.72-0.79)	0.21 (0.20-0.23)
July	0.56 (0.53-0.58)	0.14 (0.13-0.15)
August	0.48 (0.46-0.50)	0.13 (0.12-0.14)
September	0.76 (0.72-0.79)	0.22 (0.21-0.24)
October	0.86 (0.82-0.89)	0.33 (0.31-0.35)
November	0.96 (0.92-1.00)	0.75 (0.71-0.79)
December	1.16 (1.11-1.20)	1.35 (1.29-1.41)
Male sex (reference = female)	1.33 (1.31-1.36)	1.25 (1.22-1.29)
Age 5-12 years (reference = 0-4 years)	0.10 (0.09-0.10)	0.05 (0.05-0.05)
Region (reference = North)		
South-West	0.85 (0.84-0.87)	0.87 (0.84-0.89)
South-East	0.81 (0.79-0.83)	1.04 (1.01-1.08)
Living in urban area (reference = rural)	1.00 (0.97-1.02)	1.00 (0.97-1.03)
Socio-economic status (reference = Quintile 1)		
Quintile 2	1.14 (1.11-1.17)	1.06 (1.02-1.11)
Quintile 3	1.16 (1.13-1.20)	1.10 (1.05-1.14)
Quintile 4	1.30 (1.26-1.34)	1.18 (1.13-1.22)
Quintile 5 (most deprived)	1.33 (1.30-1.38)	1.34 (1.28-1.39)
PCV vaccination received (reference = not received)	0.69 (0.67-0.72)	0.23 (0.22-0.24)
Nov 2003 (outlier)	1.95 (1.77-2.14)	Not in model

*p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine; RTI = respiratory tract infection

Supplementary Table S2. Multivariable negative binomial regression model for acute respiratory tract infection events stratified according to sex

Characteristic	Event rate ratio (ERR (95%CI))	
	Males	Females
Time (per year increase)	1.01 (1.01-1.01)	1.02 (1.01-1.02)
Smoke-free legislation	1.23 (1.18-1.28)*	1.26 (1.20-1.31)*
Time since smoke-free legislation (per year increase)	1.06 (1.05-1.07)*	1.05 (1.04-1.06)*
Month (reference = January)		
February	0.84 (0.80-0.88)	0.82 (0.78-0.87)
March	0.80 (0.76-0.84)	0.76 (0.72-0.80)
April	0.56 (0.53-0.59)	0.51 (0.49-0.54)
May	0.55 (0.52-0.58)	0.48 (0.46-0.51)
June	0.50 (0.47-0.53)	0.41 (0.39-0.44)
July	0.34 (0.33-0.36)	0.31 (0.29-0.33)
August	0.30 (0.29-0.32)	0.27 (0.25-0.29)
September	0.51 (0.48-0.54)	0.41 (0.39-0.44)
October	0.61 (0.58-0.64)	0.52 (0.49-0.55)
November	0.87 (0.82-0.92)	0.82 (0.77-0.86)
December	1.29 (1.23-1.35)	1.24 (1.17-1.30)
Age 5-12 years (reference = 0-4 years)	0.07 (0.07-0.07)	0.08 (0.08-0.08)
Region (reference = North)		
South-West	0.87 (0.85-0.89)	0.87 (0.85-0.90)
South-East	0.91 (0.89-0.94)	0.89 (0.87-0.92)
Living in urban area (reference = rural)	0.99 (0.97-1.02)	0.99 (0.96-1.02)
Socio-economic status (reference = Quintile 1)		
Quintile 2	1.12 (1.08-1.16)	1.10 (1.06-1.14)
Quintile 3	1.14 (1.11-1.18)	1.14 (1.10-1.18)
Quintile 4	1.24 (1.20-1.28)	1.27 (1.23-1.32)
Quintile 5 (most deprived)	1.32 (1.27-1.36)	1.40 (1.34-1.45)
PCV vaccination received (reference = not received)	0.43 (0.41-0.45)	0.47 (0.44-0.49)
Nov 2003 (outlier)	1.43 (1.29-1.58)	1.55 (1.39-1.73)

*p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine

Supplementary Table S3. Multivariable negative binomial regression model for acute respiratory tract infection events stratified according to age group

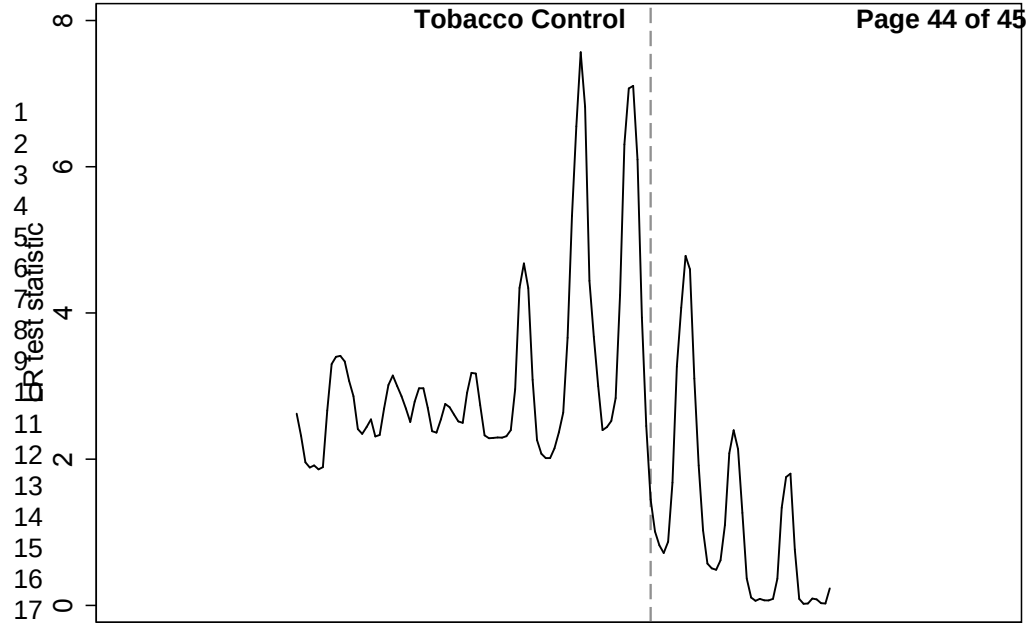
Characteristic	Event rate ratio (ERR (95%CI))	
	Age = 0-4 years	Age = 5-12 years
Time (per year increase)	1.01 (1.01-1.02)	1.02 (1.01-1.03)
Smoke-free legislation	1.30 (1.25-1.35)*	1.36 (1.27-1.45)*
Time since smoke-free legislation (per year increase)	1.08 (1.07-1.08)*	0.90 (0.89-0.92)*
Month (reference = January)		
February	0.79 (0.76-0.82)	1.03 (0.95-1.12)
March	0.72 (0.70-0.75)	1.11 (1.03-1.20)
April	0.51 (0.49-0.53)	0.66 (0.61-0.72)
May	0.48 (0.46-0.50)	0.70 (0.65-0.76)
June	0.41 (0.40-0.43)	0.72 (0.66-0.78)
July	0.30 (0.29-0.31)	0.50 (0.46-0.55)
August	0.26 (0.25-0.28)	0.44 (0.41-0.48)
September	0.42 (0.40-0.44)	0.74 (0.68-0.80)
October	0.53 (0.51-0.55)	0.78 (0.72-0.85)
November	0.82 (0.78-0.85)	0.98 (0.91-1.06)
December	1.27 (1.22-1.32)	1.23 (1.14-1.32)
Male sex (reference = female)	1.34 (1.32-1.35)	1.17 (1.13-1.21)
Region (reference = North)		
South-West	0.88 (0.86-0.90)	0.85 (0.82-0.89)
South-East	0.91 (0.89-0.93)	0.89 (0.85-0.93)
Living in urban area (reference = rural)	0.99 (0.87-1.02)	0.98 (0.94-1.02)
Socio-economic status (reference = Quintile 1)		
Quintile 2	1.10 (1.07-1.13)	1.15 (1.09-1.22)
Quintile 3	1.12 (1.09-1.15)	1.22 (1.15-1.29)
Quintile 4	1.23 (1.20-1.27)	1.31 (1.24-1.38)
Quintile 5 (most deprived)	1.34 (1.30-1.38)	1.36 (1.29-1.44)
PCV vaccination received (reference = not received)	0.38 (0.37-0.40)	2.14 (1.98-2.32)
Nov 2003 (outlier)	1.53 (1.40-1.66)	1.33 (1.10-1.61)

*p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine

Supplementary Table S4. Multivariable negative binomial regression model for acute respiratory tract infection events in South-East Scotland with adjustment for air quality

Characteristic	Event rate ratio (ERR (95%CI))
Time (per year increase)	0.99 (0.98-1.01)
Smoke-free legislation	1.25 (1.19-1.32)*
Time since smoke-free legislation (per year increase)	1.08 (1.06-1.10)*
Month (reference = January)	
February	0.82 (0.76-0.87)
March	0.76 (0.71-0.82)
April	0.53 (0.49-0.58)
May	0.52 (0.48-0.57)
June	0.44 (0.40-0.48)
July	0.32 (0.29-0.35)
August	0.26 (0.24-0.29)
September	0.43 (0.39-0.46)
October	0.54 (0.50-0.58)
November	0.80 (0.74-0.86)
December	1.26 (1.18-1.36)
Male sex (reference = female)	1.30 (1.26-1.33)
Age 5-12 years (reference = 0-4 years)	0.08 (0.08-0.08)
Living in urban area (reference = rural)	0.83 (0.80-0.86)
Socio-economic status (reference = Quintile 1)	
Quintile 2	1.17 (1.12-1.23)
Quintile 3	1.29 (1.23-1.35)
Quintile 4	1.41 (1.35-1.47)
Quintile 5 (most deprived)	1.38 (1.32-1.44)
PCV vaccination received (reference = not received)	0.50 (0.48-0.54)
Air quality indicators	
Carbon monoxide (CO; per mg/m^3)	0.88 (0.74-1.03)
Nitric oxide (NO; per µg/m^3)	0.95 (0.93-0.97)
Nitrogen dioxide (NO_2; per µg/m^3)	0.96 (0.95-0.98)
Nitrogen oxides as NO_2 (per µg/m^3)	1.03 (1.02-1.05)
Sulphur dioxide (SO_2; per µg/m^3)	0.99 (0.99-1.00)
Ozone (O_3; per µg/m^3)	0.99 (0.99-1.00)
Particulate matter of diameter <10µm (PM10; per µg/m^3)	1.01 (1.00-1.01)

*p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine



Supplementary Table S5. Multivariable negative binomial regression model for acute respiratory tract infection events with November 2004 breakpoint instead of timing of smoke-free legislation

Characteristic	Event rate ratio (ERR (95%CI))
Time (per year increase)	0.99 (0.99-1.00)
Smoke-free legislation	Not in model
Time since smoke-free legislation (per year increase)	Not in model
November 2004 breakpoint	1.23 (1.20-1.27)*
Time since November 2004 breakpoint (per year increase)	1.08 (1.07-1.09)*
Month (reference = January)	
February	0.83 (0.80-0.86)
March	0.78 (0.75-0.81)
April	0.54 (0.53-0.57)
May	0.52 (0.51-0.54)
June	0.46 (0.45-0.48)
July	0.33 (0.32-0.35)
August	0.29 (0.28-0.31)
September	0.47 (0.45-0.49)
October	0.58 (0.55-0.60)
November	0.85 (0.82-0.89)
December	1.27 (1.22-1.31)
Male sex (reference = female)	1.30 (1.28-1.33)
Age 5-12 years (reference = 0-4 years)	0.07 (0.07-0.08)
Region (reference = North)	
South-West	0.87 (0.85-0.89)
South-East	0.90 (0.89-0.93)
Living in urban area (reference = rural)	0.99 (0.98-1.01)
Socio-economic status (reference = Quintile 1)	
Quintile 2	1.11 (1.09-1.14)
Quintile 3	1.14 (1.11-1.17)
Quintile 4	1.25 (1.22-1.29)
Quintile 5 (most deprived)	1.35 (1.31-1.39)
PCV vaccination received (reference = not received)	0.45 (0.43-0.46)
Nov 2003 (outlier)	1.61 (1.49-1.74)

*p<0.001 (p-value only indicated for smoke-free legislation indicators); PCV = pneumococcal conjugate vaccine